

WHAT IS CLAIMED IS:

1. A combination, comprising:
 - a) an oxidizing agent or a reducing agent;
 - b) a protein denaturing agent; and
 - c) a hapten.

2. The combination of claim 1, wherein the oxidizing or reducing agent, the protein denaturing agent and the hapten are formulated in a single pharmaceutical composition or each is formulated in a separate pharmaceutical composition.

3. The combination of claim 1, wherein the oxidizing agent is selected from the group consisting of hydrogen peroxide (H_2O_2), ozone (O_3), polyatomic oxygen O_7 , polyatomic oxygen O_8 , $NaIO_4$, potassium peroxymonosulfate (oxone), D,L-S-methylipoic acid methyl ester, tertiary butyl hydroperoxide, menadione, diamide, iodogen, N-bromosuccinimide, omeprazole and N-ethylmaleimide.

4. The combination of claim 1, wherein the reducing agent is selected from the group consisting of hematoxylin, a hypoxic reducing agent, and nonnitro compound tirapazamine (SR-4233).

5. The combination of claim 4, wherein the hypoxic reducing agent is a nitroimidazole.

6. The combination of claim 1, wherein the protein denaturing agent is selected from the group consisting of an alcohol, guanidine hydrochloride, guanidinium thiocyanate, sodium citrate, 2-mercaptoethanol, the ionic detergent sarcosyl, phenol, chloroform and urea.

7. The combination of claim 6, wherein the alcohol is selected from the group consisting of methyl, ethyl, *n*-propyl, *n*-butyl, *n*-pentyl, *n*-hexyl, *n*-heptyl, *n*-octyl, *n*-decyl, *n*-dodecyl, *n*-tetradecyl, *n*-hexadecyl, *n*-octadecyl, isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, isopentyl, *active*-amyl, *tert*-pentyl, cyclopentanol, cyclohexanol, allyl, crotyl, methylvinylmethanol, benzyl, α -phenylethyl, β -phenylethyl, diphenylmethanol, triphenylmethanol, cinnamyl, 1,2-ethanediol, 1,2-propanediol, 1,3-propanediol, glycerol and pentaerythritol alcohol.

8. The combination of claim 7, wherein the alcohol is ethanol.

9. The combination of claim 1, wherein the hapten is selected from the group consisting of trinitrophenol (TNP), dinitrophenol (DNP), N-iodoacetyl-N'-(5-sulfonic 1-naphthyl) ethylene diamine (AED), dinitrofluorobenzene(DNFB) and Ovabulin (OVA).

10. The combination of claim 1, further comprising an anti-neoplasm agent.

11. The combination of claim 10, wherein the anti-neoplasm agent is an anti-angiogenic agent.

12. The combination of claim 11, wherein the anti-angiogenic agent is selected from the group consisting of an inhibitor of basement membrane degradation, an inhibitor of cell migration, an inhibitor of endothelial cell proliferation, an inhibitor of three-dimensional organization and establishment of potency.

13. The combination of claim 11, wherein the anti-angiogenic agent is selected from the group consisting of an angiostatic gene, an angiostatic chemokine gene, AGM-1470 (TNP-470), angiostatic steroids, angiostatin, antibodies against $\alpha\text{v}\beta_3$, antibodies against bFGF, antibodies against IL-1, antibodies against TNF- α , antibodies against VEGF, auranofin, azathioprine, BB-94, BB-2516, basic FGF-soluble receptor, carboxyamido-trizole (CAI), cartilage-derived inhibitor (CDI), chitin, chloroquine, cisplatin, CM 101, cortisone/heparin, cortisone/hyaluroflan, cortexolone/heparin, CT-2584, cyclophosphamide, cyclosporin A, dexamethasone, diclofenac/hyaluronan, eosinophilic major basic protein, fibronectin peptides, gelatinase inhibitor, glioma-derived angiogenesis inhibitory factor (GD-AIF), GM 1474, gold chloride, gold thiomalate, heparinases, hyaluronan (high and low molecular-weight species), hydrocortisone/beta-cyclodextran, ibuprofen, indomethacin, interferon-alpha, interferon gamma-inducible protein 10, interferon-gamma, IL-1, IL-2, IL-4, IL-12, laminin, levamisole, linomide, LM609, matrix metalloproteinase inhibitor, marimastat (BB-2516), medroxyprogesterone, 6-methylmercaptapurine riboside, metastat (Col-3), methotrexate, minocycline, nitric oxide, octreotide (somatostatin analogue), Paclitaxel, D-penicillamine, pentosan polysulfate, placental proliferin-related protein, placental Rnase inhibitor, plasminogen activator inhibitor (PAIs), platelet factor-4 (PF4), prednisolone, prolactin (16-Kda fragment), proliferin-related protein, prostaglandin synthase inhibitor, protamine, retinoids, Roquinimex (LS-2616. linomide), somatostatin, stromelysin inhibitor, substance P, suramin, SU101, tecogalan sodium (DS-4152), tetrahydrocortisol-

stthrombospondins (TSPs), tissue inhibitor of metalloproteinases (TIMP 1, 2, 3), vascular endothelial growth factor inhibitors, vitamin A, Vitaxin and vitreous fluids.

14. The combination of claim 10, wherein the anti-neoplasm agent is selected from the group consisting of an alkylating agent, an antimetabolite, a natural product, a platinum coordination complex, an anthracenedione, a substituted urea, a methylhydrazine derivative, an adrenocortical suppressant, a hormone, an antagonist, an anti-cancer polysaccharide and an anti-cancer herb extract.

15. The combination of claim 10, wherein the anti-neoplasm agent is an oncogene inhibitor or a tumor suppressor gene or protein.

16. The combination of claim 15, wherein the oncogene inhibitor is an anti-oncogene antibody or an anti-oncogene antisense oligonucleotide.

17. The combination of claim 15, wherein the oncogene is selected from the group consisting of *abl*, *erbA*, *erbB*, *ets*, *fes (fps)*, *fgr*, *fms*, *fos*, *hst*, *int1*, *int2*, *jun*, *hit*, *B-lym*, *mas*, *met*, *mil (raf)*, *mos*, *myb*, *myc*, *N-myc*, *neu (ErbB2)*, *ral (mil)*, *Ha-ras*, *Ki-ras*, *N-ras*, *rel*, *ros*, *sis*, *src*, *ski*, *trk* and *yes*.

18. The combination of claim 15, wherein the tumor suppressor gene is selected from the group consisting of *p16*, *p21*, *p27*, *p53*, *RB*, *WT-1*, *DCC*, *NF-1* and *APC*.

19. The combination of claim 1, further comprising a viral vector carrying an oncogene or a tumor suppressor gene sequence.

20. The combination of claim 19, wherein the viral vector is selected from the group consisting of an adenovirus vector, a simian virus vector, a conditionally replicating human immunodeficiency viral vector, a retrovirus vector, a SV40 vector, a Herpes simplex viral amplicon vector and a Vaccinia virus vector.

21. The combination of claim 1, further comprising a facilitating agent that facilitates conjugation between the hapten and a tumor antigen.

22. The combination of claim 21, wherein the facilitating agent is a chelator or a chemical linking agent.

23. The combination of claim 22, wherein the chelator is glycylytyrosyl-(N-e-diethylenetri-aminepetaacetic acid)-lysine (GYK-DTPA) or doxorubicin adipic-dihydrazide (ADR-ADH).

24. The combination of claim 22, wherein the chemical linking agent is carbodiimide.

25. The combination of claim 1, further comprising an immune response potentiator.

26. The combination of claim 25, wherein the immune response potentiator is selected from the group consisting of Bacille Calmette-Guerin (BCG), Corynebacterium Parvum, Brucella abortus extract, glucan, levamisole, tilorone, an enzyme and a non-virulent virus.

27. The combination of claim 26, wherein the enzyme is selected from the group consisting of Vibrio cholera neuraminidase (VCN), Papain, β -Gal and ConA.

28. The combination of claim 26, wherein the non-virulent virus is a non-virulent Newcastle virus.

29. The combination of claim 1, further comprising a coagulation lysing agent.

30. The combination of claim 29, wherein the coagulation lysing agent is selected from the group consisting of proteinase K, Glycosyl-phosphatidylinositol-B7 and pancreatin.

31. The combination of claim 1, wherein the oxidizing agent is H_2O_2 , the protein denaturing agent is ethanol and the hapten is TNP.

32. The combination of claim 21, wherein the oxidizing agent is H_2O_2 , the protein denaturing agent is ethanol, the hapten is TNP and the facilitating agent is carbodiimide.

33. The combination of claim 1, wherein the oxidizing agent or reducing agent is from about 0.01% (w/w) to about 35% (w/w), the protein denaturing agent is from about 1% (w/w) to about 99% (w/w) and the hapten is from about 1 mg/ml to about 80 mg/ml.

34. A kit, comprising the combination of claim 1.

35. An article of manufacture, comprising:

- a) packaging material;
- b) the combination of claim 1; and
- c) a label indicating that the article is for treating neoplasms.

36. A method for treating neoplasm in a mammal, comprising *in situ* administering to neoplasm of a mammal an effective amount of a hapten and coagulation agent(s) or treatment(s) that causes coagulation of the neoplasm, whereby an autologous immune response is generated against the neoplasm and the neoplasm is treated.

37. The method of claim 36, wherein the mammal is a human.

38. The method of claim 36, wherein the hapten is selected from the group consisting of trinitrophenol (TNP), drinitrophenyl (DNP), N-iodoacetyl-N'-(5-sulfonic 1-naphthyl) ethylene diamine (AED), dinitrofluorobenzene(DNFB) and Ovabulin (OVA).

39. The method of claim 36, further comprising administering to neoplasm a facilitating agent that facilitates conjugation between the hapten and a tumor antigen of the neoplasm.

40. The method of claim 39, wherein the facilitating agent is a chelator or a chemical linking agent.

41. The method of claim 40, wherein the chelator is glycylytyrosyl-(N-e-diethylenetri-aminepetaacetic acid)-lysine (GYK-DTPA) or doxorubicin adipic-dihydrazide (ADR-ADH).

42. The method of claim 40, wherein the chemical linking agent is carbodiimide.

43. The method of claim 36, further comprising administering an immune response potentiator to the neoplasm.

44. The method of claim 43, wherein the immune response potentiator is selected from the group consisting of Bacille Calmette-Guerin (BCG), Corynebacterium Parvum, Brucella abortus extract, glucan, levamisole, tilorone, an enzyme, a non-virulent virus, a polysaccharide and a herb extract.

45. The method of claim 44, wherein the enzyme is selected from the group consisting of Vibrio cholera neuraminidase (VCN), Papain, β -Gal and ConA.

46. The method of claim 44, wherein the non-virulent virus is a non-virulent Newcastle virus.

47. The method of claim 36, further comprising administering a coagulation lysing agent to the neoplasm.

48. The method of claim 47, wherein the coagulation lysing agent is selected from the group consisting of proteinase K, Glycosyl-phosphatidylinositol-B7 and pancreatin.

49. The method of claim 36, wherein the coagulation agent(s) is a combination comprising:

- a) an oxidizing agent or a reducing agent; and
- b) a protein denaturing agent.

50. The method of claim 49, wherein the oxidizing or reducing agent, the protein denaturing agent and the hapten are formulated in a single pharmaceutical composition or each is formulated in a separate pharmaceutical composition.

51. The method of claim 49, wherein the oxidizing agent is selected from the group consisting of hydrogen peroxide (H₂O₂), ozone, polyatomic oxygen O₇, polyatomic oxygen O₈, NaIO₄, potassium peroxy monosulfate (oxone), D,L-S-methylipoic acid methyl ester, tertiary butyl hydroperoxide, menadione, diamide, iodogen, N-bromosuccinimide, omeprazole and N-ethylmaleimide.

52. The method of claim 49, wherein the reducing agent is selected from the group consisting of hematoxylin, a hypoxic reducing agent, and nonnitro compound SR 4233.

53. The method of claim 52, wherein the hypoxic reducing agent is a nitroimidazole.

54. The method of claim 49, wherein the protein denaturing agent is selected from the group consisting of an alcohol, guanidine hydrochloride, guanidinium thiocyanate, sodium citrate, 2-mercaptoethanol, sarcosyl, phenol, chloroform and urea.

55. The method of claim 54, wherein the alcohol is selected from the group consisting of methyl, ethyl, *n*-propyl, *n*-butyl, *n*-pentyl, *n*-hexyl, *n*-heptyl, *n*-octyl, *n*-decyl, *n*-dodecyl, *n*-tetradecyl, *n*-hexadecyl, *n*-octadecyl, isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, isopentyl, *active*-amyl, *tert*-pentyl, cyclopentanol, cyclohexanol, allyl, crotyl, methylvinylmethanol, benzyl, α -phenylethyl, β -phenylethyl, diphenylmethanol, triphenylmethanol, cinnamyl, 1,2-ethanediol, 1,2-propanediol, 1,3-propanediol, glycerol and pentaerythritol alcohol.

56. The method of claim 55, wherein the alcohol is ethanol.

57. The method of claim 49, wherein the combination further comprises an anti-neoplasm agent.

58. The method of claim 57, wherein the anti-neoplasm agent is an anti-angiogenic agent.

59. The method of claim 58, wherein the anti-angiogenic agent is selected from the group consisting of an inhibitor of basement membrane degradation, an inhibitor of cell migration, an inhibitor of endothelial cell proliferation, an inhibitor of three-dimensional organization and establishment of potency.

60. The method of claim 58, wherein the anti-angiogenic agent is selected from the group consisting of an angiostatic gene, an angiostatic chemokine gene, AGM-1470 (TNP-470), angiostatic steroids, angiostatin, antibodies against $\alpha v\beta 3$, antibodies against bFGF, antibodies against IL-1, antibodies against TNF- α , antibodies against VEGF, auranofin, azathioprine, BB-94, BB-2516, basic FGF-soluble receptor, carboxyamido-trizole (CAI), cartilage-derived inhibitor (CDI), chitin, chloroquine, cisplatin, CM 101, cortisone/heparin, cortisone/hyaluroflan, cortexolone/heparin, CT-2584, cyclophosphamide, cyclosporin A, dexamethasone, diclofenac/hyaluronan, eosinophilic major basic protein, fibronectin peptides, gelatinase inhibitor, glioma-derived angiogenesis inhibitory factor (GD-AIF), GM 1474, gold chloride, gold thiomalate, heparinases, hyaluronan (high and low molecular-weight species), hydrocortisone/beta-cyclodextran, ibuprofen, indomethacin, interferon-alpha, interferon gamma-inducible protein 10, interferon-gamma, IL-1, IL-2, IL-4, IL-12, laminin, levamisole, linomide, LM609, matrix metalloproteinase inhibitor, marimastat (BB-2516), medroxyprogesterone, 6-methylmercaptopurine riboside, metastat (Col-3), methotrexate, minocycline, nitric oxide, octreotide (somatostatin analogue), Paclitaxel, D-penicillamine, pentosan polysulfate, placental proliferin-related protein, placental Rnase inhibitor, plasminogen activator inhibitor (PAIs), platelet factor-4 (PF4), prednisolone, prolactin (16-Kda fragment), proliferin-related protein, prostaglandin synthase inhibitor, protamine, retinoids, Roquinimex (LS-2616, linomide), somatostatin, stromelysin inhibitor, substance P, suramin, SU101, tecogalan sodium (DS-4152), tetrahydrocortisol-sthrombospondins (TSPs), tissue inhibitor of metalloproteinases (TIMP 1, 2, 3), vascular endothelial growth factor inhibitors, vitamin A, Vitaxin and vitreous fluids.

61. The method of claim 57, wherein the anti-neoplasm agent is selected from the group consisting of an alkylating agent, an antimetabolite, a natural product, a platinum coordination complex, an anthracenedione, a substituted urea, a methylhydrazine derivative, an adrenocortical suppressant, a hormone and an antagonist.

5 62. The method of claim 57, wherein the anti-neoplasm agent is an oncogene inhibitor or a tumor suppressor gene or protein.

63. The method of claim 62, wherein the oncogene inhibitor is an anti-oncogene antibody or an anti-oncogene antisense oligonucleotide.

10 64. The method of claim 62, wherein the oncogene is selected from the group consisting of *abl*, *erbA*, *erbB*, *ets*, *fes* (*fps*), *fgr*, *fms*, *fos*, *hst*, *int1*, *int2*, *jun*, *hit*, *B-lym*, *mas*, *met*, *mil* (*raf*), *mos*, *myb*, *myc*, *N-myc*, *neu* (*ErbB2*), *ral* (*mil*), *Ha-ras*, *Ki-ras*, *N-ras*, *rel*, *ros*, *sis*, *src*, *ski*, *trk* and *yes*.

15 65. The method of claim 62, wherein the tumor suppressor gene is selected from the group consisting of *p16*, *p21*, *p27*, *p53*, *RB*, *WT-1*, *DCC*, *NF-1* and *APC*.

66. The method of claim 49, wherein the combination further comprises a viral vector carrying an oncogene or a tumor suppressor gene sequence.

20 67. The method of claim 66, wherein the viral vector is selected from the group consisting of an adenovirus vector, a simian virus vector, a conditionally replicating human immunodeficiency viral vector, a retrovirus vector, a SV40 vector, a Herpes simplex viral amplicon vector and a Vaccinia virus vector.

68. The method of claim 49, wherein the oxidizing agent is H₂O₂, the protein denaturing agent is ethanol and the hapten is TNP.

25 69. The method of claim 49, wherein the oxidizing agent or reducing agent is from about 0.01% (w/w) to about 35% (w/w), the protein denaturing agent is from about 1% (w/w) to about 99% (w/w) and the hapten is from about 1 mg/ml to about 80 mg/ml.

70. The method of claim 36, wherein the coagulation treatment is selected from the group consisting of cryotherapy, laser coagulation (ILC), percutaneous microwave coagulation therapy, radio-frequency-induced coagulation necrosis, transpupillary thermotherapy, ultrasonictherapy and radiationtherapy.

71. The method of claim 36, wherein the autologous immune response generated by the combined action of the hapten and the coagulation agent or treatment comprises or is a humoral and/or cellular immune response.

72. The method of claim 36, wherein the neoplasm to be treated is selected from the group consisting of adrenal gland, anus, auditory nerve, bile ducts, bladder, bone, brain, breast, brucella, central nervous system, cervix, colon, ear, endometrium, esophagus, eye, eyelids, fallopian tube, gastrointestinal tract, head and neck, heart, kidney, larynx, liver, lung, mandible, mandibular condyle, maxilla, mouth, nasopharynx, nose, oral cavity, ovary, pancreas, parotid gland, penis, pinna, pituitary, prostate gland, rectum, retina, salivary glands, skin, small intestine, spinal cord, stomach, testes, thyroid, tonsil, urethra, uterus, vagina, vestibulocochlear nerve and vulva neoplasm.

73. The method of claim 36, wherein the neoplasm to be treated is a solid tumor.

74. The method of claim 73, wherein the size of the solid tumor is larger than 10^8 cells.

75. The method of claim 74, wherein the size of the solid tumor is from about 5×10^9 to about 10^{11} cells.

76. The method of claim 36, wherein the hapten and the coagulation agent(s) are administered to the neoplasm via injection.

77. The method of claim 36, wherein the hapten and the coagulation agent(s) are administered to the neoplasm in combination with a surgical procedure.

78. The combination of claim 1, further comprising a molecule selected from the group consisting of a suicide gene sequence, a cytolytic gene sequence, a cytokine gene sequence, a radiation sensitizer, a cytokine-containing depot, a reporter and a reporter gene sequence.

79. The method of claim 36, further comprising *in situ* administering a molecule selected from the group consisting of a suicide gene sequence, a cytolytic gene sequence, a cytokine gene sequence, a radiation sensitizer, a cytokine-containing depot, a reporter and a reporter gene sequence.